

EXHIBIT E

FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)

Get updates on the recalls

[Search ARB Recalls List \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan\)](#)

[FDA's Assessment of Currently Marketed ARBs \(/drugs/drug-safety-and-availability/fdas-assessment-currently-marketed-arb-drug-products\)](#)

Where can I get more information?

[Overview of ARB Recalls \(/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan\)](#)

[More Q&A on ARB Recalls \(/drugs/drug-safety-and-availability/more-questions-and-answers-impurities-found-certain-angiotensin-ii-receptor-blocker-arb-products\)](#)

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3/18/2022
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UPDATES & PRESS ANNOUNCEMENTS

Update: 9/20/2019 - Torrent expands its voluntary recall of losartan

Update [9/20/2019] Torrent Pharmaceuticals is expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-o) to include five additional lots of losartan potassium tablets (three lots of losartan potassium tablets and two lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited. Torrent is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of recalled angiotensin II receptor blockers (ARBs) (/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

8/28/2019: STATEMENT: Statement on the agency's ongoing efforts to resolve safety issue with ARB medications

6/26/2019: UPDATE - Macleods Pharmaceuticals voluntarily recalls losartan containing NMBA

6/12/2019: UPDATE - Teva expands its voluntary recall of losartan

5/6/2019: UPDATE - FDA alerts patients and health care professionals to Vivimed's recall of losartan medication due to NMBA

5/2/2019: UPDATE - Laboratory analysis of valsartan products

4/29/2019: UPDATE - FDA alerts patients and health care professionals to Teva's recall and Legacy's expanded recall of losartan medication due to NMBA

4/19/2019: UPDATE - Torrent further expands its voluntary recall of losartan; FDA posts new nitrosamine testing methods

4/4/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the agency's list of known nitrosamine-free valsartan and ARB class medicines, as part of agency's ongoing efforts to resolve ongoing safety issue

3/22/2019: UPDATE - FDA updates recalled valsartan-containing and losartan-containing medicine information

3/20/2019: UPDATE - FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market

3/1/2019: UPDATE - Torrent again expands its voluntary recall of losartan; Hetero also voluntarily recalls losartan

3/1/2019: UPDATE - Aurobindo expands its voluntary recall of valsartan and amlodipine/valsartan

3/1/2019: PRESS RELEASE - FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall

FDA updates table of interim limits for nitrosamine impurities in ARBs

Update [2/28/2019] FDA is posting the updated table of interim acceptable intake limits for nitrosamine impurities to reflect N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) limits, which are the same as those for NDMA.

The agency will use the interim limits below to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

Not all ARB products contain NDMA, NDEA or NMBA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

Interim Limits for NDMA, NDEA, and NMBA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**	Acceptable Intake NMBA (ng/day)*	Acceptable Intake NMBA (ppm)**
Valsartan	320	96	0.3	26.5	0.083	96	0.3
Losartan	100	96	0.96	26.5	0.27	96	0.96***
Irbesartan	300	96	0.32	26.5	0.088	96	0.32
Azilsartan	80	96	1.2	26.5	0.33	96	1.2
Olmesartan	40	96	2.4	26.5	0.66	96	2.4
Eprosartan	800	96	0.12	26.5	0.033	96	0.12

Candesartan	32	96	3.0	26.5	0.83	96	3.0
Telmisartan	80	96	1.2	26.5	0.33	96	1.2

* The acceptable intake is a daily exposure to a compound such as NDMA, NDEA, or NMBA that approximates a 1:100,000 cancer risk after 70 years exposure

** These values are based on a drug's maximum daily dose as reflected in the drug label

*** FDA is temporarily not objecting to losartan with NMBA below 9.82 ppm remaining on the market

2/25/2019: UPDATE - Losartan distributed by Macleods Pharmaceuticals voluntarily recalled



1/25/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues



1/23/2019: UPDATE - Torrent further expands its voluntary recall of losartan



1/18/2019: UPDATE - Irbesartan distributed by Solco Healthcare voluntarily recalled



1/3/2019: UPDATE - Torrent expands its voluntary recall of losartan



1/2/2019: UPDATE - FDA alerts patients and health care professionals to Aurobindo's recall of valsartan medication due to NDEA



12/20/2019: UPDATE - FDA alerts patients and health care professionals to Torrent's recall of losartan medication due to NDEA



12/19/2018: UPDATE - FDA presents interim limits of nitrosamines in currently marketed ARBs



12/12/2018: UPDATE - FDA updates NDMA and NDEA detection methods, announces posting of ZHP warning letter



12/11/2018: PRESS RELEASE - FDA warns API manufacturer involved in valsartan recall, provides information for patients taking these medications



12/6/2018: UPDATE - Mylan expands its voluntary recall of valsartan-containing products



11/27/2018: UPDATE - FDA alerts patients and health care professionals to Teva's recall of valsartan products due to NDEA



11/21/2018: UPDATE - FDA alerts patients and health care professionals to Mylan's recall of valsartan products due to NDEA



11/9/2018: UPDATE - FDA alerts patients and health care professionals to Sandoz's losartan potassium and hydrochlorothiazide recall of one lot due to NDEA



10/30/2018: UPDATE - FDA alerts patients and health care professionals to ScieGen's irbesartan recall due to NDEA



10/24/2018: UPDATE - FDA updates recalled valsartan-containing product information 

10/16/2018: UPDATE - FDA releases additional NDMA/NDEA detection method 

10/11/2018: UPDATE - FDA releases method for detection and quantification of both NDMA and NDEA 

10/5/2018: UPDATE - FDA posts laboratory analysis of NDMA levels in recalled valsartan products 

9/28/2018: UPDATE - FDA places Zhejiang Huahai Pharmaceuticals on import alert 

9/24/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan 

9/13/2018: PRESS RELEASE - FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products 

8/30/2018: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings 

8/24/2018: UPDATE - FDA updates recall lists 

8/22/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan 

8/20/2018: UPDATE - FDA updates recalled valsartan-containing product information and presents NDMA levels in some foods 

8/9/2018: UPDATE - FDA updates recalled valsartan-containing product information 

8/2/2018: UPDATE - FDA updates recalled valsartan-containing product information and reminds API manufacturers to evaluate processes for unsafe impurities 

7/27/2018: UPDATE - FDA updates recalled valsartan-containing product information 

7/27/2018: UPDATE - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S. 

7/24/2018: UPDATE - FDA publishes a list of valsartan-containing products not part of the recall 

7/18/2018: STATEMENT - FDA updates health care professionals and patients on recent valsartan recalls 

7/13/2018: PRESS RELEASE - FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity 

FDA-published testing methods to provide options for regulators and industry to detect NDMA and NDEA impurities

The links below are to FDA-published testing methods to provide options for regulators and industry to detect nitrosamine impurities in ARB drug substances and drug products. These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API

or drug product, or if the results are used in a regulatory submission.

- Combined headspace method (/media/117843/download): a GC/MS method that allows determination of both N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) simultaneously
- Combined direct injection method (/media/117807/download): a GC-MS/MS method that allows for determination of both NDMA and NDEA simultaneously
- Direct injection GC-MS method (/media/123409/download): a method that can detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- Headspace GC-MS method (/media/124025/download): a method that can detect NDMA, NDEA, NDIPA, and NEIPA
- LC-HRMS method (/media/125478/download): a method that can detect NDMA, NDEA, NEIPA, NDIPA, NDBA, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)
- RapidFire-MS/MS method (/media/125477/download): a method that can detect NEIPA, NDIPA, NDBA, and NMBA. We do not recommend using this method to detect NDMA or NDEA because it is less sensitive to those impurities.

The LC-HRMS and RapidFire-MS/MS methods are the first methods FDA has posted for detecting NMBA. The European Directorate for the Quality of Medicines (EDQM) has also published methods to detect NDMA and NDEA (<https://www.edqm.eu/en/ad-hoc-projects-omcl-network>) (http://www.fda.gov/about-fda/website-policies/website-disclaimer). FDA has not validated EDQM's methods.

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